Defining the Isoform-Specific Effects of Apolipoprotein E on the Development of iPS Cells into Functional Neurons in Vitro and in Vivo

Grant Award Details

Defining the Isoform-Specific Effects of Apolipoprotein E on the Development of iPS Cells into Functional Neurons in Vitro and in Vivo

Grant Type: New Faculty II

Grant Number: RN2-00952

Project Objective: to determine the role of apoE isoforms in neuronal development from iPSC

Investigator:

Name:	Yadong Huang
Institution:	Gladstone Institutes, J. David
Type:	PI

Disease Focus: Neurological Disorders, Stroke

Human Stem Cell Use: iPS Cell

Cell Line Generation: iPS Cell

Award Value: $2,757,303

Status: Closed

Progress Reports

Reporting Period: Year 1

View Report

Reporting Period: Year 2

View Report

Reporting Period: Year 3

View Report

Reporting Period: Year 4

View Report

Reporting Period: Year 5

View Report

Grant Application Details

Application Title: Defining the Isoform-Specific Effects of Apolipoprotein E on the Development of iPS Cells into Functional Neurons in Vitro and in Vivo

Public Abstract: GOALS We propose to determine the effects of different forms of apoE on the development of induced pluripotent stem (iPS) cells into functional neurons. In Aim 1, iPS cells will be generated from skin cells of adult knock-in (KI) mice expressing different forms of human apoE and in humans with different apoE genotypes. In Aim 2, the development of the iPS cells into functional neurons in culture and in mouse brains will be compared. In Aim 3, the effects of different forms of apoE on the functional recovery of mice with acute brain injury treated with iPS cell–derived neural stem cells (NSCs) will be assessed. RATIONALE AND SIGNIFICANCE The central nervous system (CNS) has limited ability to regenerate and recover after injury. For this reason, recovery from acute and chronic neurological diseases, such as stroke and Alzheimer's disease (AD), is often incomplete and disability results. Embryonic stem cells have great promise for treating or curing neurological diseases, but their therapeutic use is limited by ethical concerns and by rejection reactions after allogenic transplantation. The generation of iPS cells from somatic cells offers a way to potentially circumvent the ethical issues and to generate patient- and disease-specific stem cells for future therapy. In the CNS, apoE plays important roles in lipid homeostasis and in neuronal maintenance. However, apoE2, apoE3, and apoE4 differ in their ability to accomplish these tasks. ApoE4, the major genetic risk factor for AD, is associated with poor clinical outcome and more rapid progression or greater severity of head trauma, stroke, Parkinson's disease, multiple sclerosis, and amyotrophic lateral sclerosis—all potential targets of stem cell therapy. This proposal builds on three novel findings in human apoE-KI mice. (1) NSCs express apoE. (2) ApoE plays a role in cell-fate determination (neuron vs astrocyte) of NSCs. (3) ApoE4 impairs the neuronal development of NSCs. Thus, we hypothesize that transplantation of iPS cells derived from apoE4 carriers (~20% of the general population and ~50% of AD patients) might not be beneficial or even detrimental for patients with neurological diseases. We propose in vitro and in vivo studies to assess the effects of different forms of apoE on the development of iPS cells into functional neurons and on the functional recovery of mice with acute brain injury treated with iPS cell-derived NSCs. These studies will shed light on the regulation of neuronal development of iPS cells and help to "optimize" future iPS cell therapy for neurological diseases. SPECIFIC AIMS Aim 1. To establish adult mouse and human iPS cell lines with different apoE genotypes. Aim 2. To determine the isoform-specific effects of apoE on the development of iPS cells into functional neurons in culture and in mouse brains. Aim 3. To assess the isoform-specific effects of apoE on the functional recovery of mice with acute (stroke) brain injury treated with iPS cell-derived NSCs.

Statement of Benefit to California:	CONTRIBUTION TO THE CALFORNIA ECONOMY: A major goal of regenerative medicine is to repair damaged cells or tissue. My research focuses on (1) understanding the role of neuronal regeneration in central nervous system function and (2) developing stem cell therapy for acute and chronic neurological diseases, including stroke and Alzheimer's disease. Stroke and Alzheimer's disease are the leading causes of disability and dementia and are the fastest growing form of neurological diseases in California, in the USA, and worldwide. My research could benefit the California economy by creating jobs in the biomedical sector. Ultimately, this study could help reduce the adverse impact of neurological diseases. Thereby, I hope to increase the productivity and enhance the quality of life for Californians. The results of my studies will also help develop new technology that could contribute to the California biotechnology industry. The studies will characterize multiple lines of induced pluripotent stem (iPS) cells carrying apoE3, a protein protective to the brain, or apoE4, which is detrimental to the brain and is associated with increased risk of Alzheimer's disease and other neurodegenerative disorders. These cell lines could be valuable for biotechnology companies and researchers who are screening for drug compounds targeting different neurological diseases. CONTRIBUTION TO THE HEALTH OF CALFORNIANS: The most important contribution of the studies will be to improve the health of Californians. Diseases that are the target of regenerative medicine, such as stroke and Alzheimer's disease, are major causes of mortality and morbidity, resulting in billions of dollars in healthcare costs and lost productivity. As we continue our efforts in medical research, we hope to one day unlock the secrets of brain development and repair. This knowledge will help medical researchers develop beneficial therapies beyond what is currently available and potentially improve the quality of life and life expectancy of patients with neurological diseases, such as stroke and Alzheimer's disease.
